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09/674,377	10/30/2000	Toshikazu Nakamura	Q 61434	7003

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EXAMINER	
ALLEN, MARIANNE P	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,377	NAKAMURA, TOSHIKAZU	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,16,28-31,33,34,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *16 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,28-31,33,34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *12, 14, 16, 28-31, 33-34, 36-37* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 2/14/08 have been fully considered but they are not persuasive.

Claims 1-11, 13, 15, 17-27, 32, and 35 have been cancelled. Claims 12, 14, 28-31, 33-34, and 36 are under consideration by the examiner.

Election/Restrictions

Claims 16 and 37 remain withdrawn from further consideration as being directed to a non-elected invention.

Applicant is reminded that only the species of "cancer" is under consideration at this time. See restriction dated 10/4/05 and election dated 11/4/05.

Claim Objections

Applicant is advised that should claim 28 be found allowable, claim 29 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

These claims appear to be identical in scope as they are both directed to administering a polypeptide having the amino acid sequence of SEQ ID NO: 2.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, 28, 30-31, 33-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

These claims remain rejected for reciting "at least one hairpin domain and four Kringle domains."

Applicant points to the substitute specification at page 13, lines 20, through page 14, line 4, in the substitute specification filed 12/6/06. The relevant parts of pages 13 and 14 are reproduced below. Emphasis has been added.

The extent of said "deletion, substitution or addition" of amino acids and the positions involved are not particularly restricted only if the mutant polypeptide still retains the above-mentioned physiological activities. By way of example, a polypeptide resulting from the deletion or addition of one or more than one (or several) amino acids in the N-terminal and/or C-terminal region of said HGF/NK4 and a polypeptide resulting from the deletion or addition of one or more than one (or several) amino acids in the intermediate region of HGF/NK4. Preferably, however, at least one hairpin domain and 4 Kringle domains, which characterize the structure of HGF/NK4, are **substantially retained** after the mutation.

As a corollary, as a typical mutant peptide, a polypeptide resulting from the substitution, deletion or addition of one or more than one (or several) of the amino acids in the region exclusive of said hairpin domain and 4 Kringle domain can be mentioned. As specific examples of such mutant peptide, there can be mentioned a polypeptide [HGF/NK4 (del 5)] resulting from the deletion of amino acids, namely amino acid Nos. 162-166 (amino acids Nos. 131~135 in SEQ ID NO:l), from the HGF/NK4 polypeptide, that it to say the polypeptide having the amino acid sequence depicted in SEQ ID NO:2.

These portions of the specification make clear that SEQ ID NO: 2 **does not** contain at least one hairpin domain and 4 Kringle domains **in their entirety** as the present claim language implies. The claims do not recite that these structures are **substantially retained** as disclosed in the specification.

As the amended claims are now limited to polypeptides having the amino acid sequence of SEQ ID NO: 2, the recitation "wherein the polypeptide has at least one hairpin domain and four Kringle domains" is an inaccurate limitation. Four **complete** Kringle domains are **not** present. Even if the claims were amended to recite "wherein the polypeptide substantially retains at least one hairpin domain and four Kringle domains," this would be an unnecessary or redundant limitation as it adds no additional structural information to the claim. This is implicit in the recitation of SEQ ID NO: 2.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 14, 28, 30-31, 33-34, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claims are confusing in reciting "having the amino acid sequence of SEQ ID NO: 2" and "wherein the polypeptide has at least one hairpin domain and four Kringle domains." Four **complete** Kringle domains are **not** present as implied by this claim language. The recitation "wherein the polypeptide has at least one hairpin domain and four Kringle domains" is an inaccurate limitation for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12, 14, 28-31, 33-34, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwall et al., U.S. Patent No. 6,207,152 (priority date 2/17/1998) in view of Date et al. (1997) and Nakamura et al. (EP 0461560, 1991).

For purposes of applying art, the claims are interpreted to require SEQ ID NO: 2 but not to require four complete Kringle domains (i.e the claim is interpreted to mean "wherein the polypeptide **substantially retains** at least one hairpin domain and four Kringle domains").

Date et al. discloses HGF variant HGF/NK4, which is the same molecule as SEQ ID NO: 1 of the instant application. The protein was used to examine the mitogenic activity on rat hepatocytes in primary culture (page 4 and Figure 3), and thus would necessarily have been in a pharmaceutically acceptable formulation. The protein was made in CHO cells. At page 31 of the specification as filed, it is disclosed that the protein, as made by CHO cells, has an N-terminus of Pyr-Glu. Date et al. does not disclose SEQ ID NO: 2.

SEQ ID NO: 2 differs from the disclosure of Date et al. in that SEQ ID NO:2 has a deletion of 5 amino acids relative to the protein of SEQ ID NO: 1.

Nakamura et al., disclose a variant of HGF comprising the same 5 amino acid deletion relative to SEQ ID NO: 1 as found in SEQ ID NO: 2, see Figure 3 and claim 3. They disclose the protein having that 5 amino acid deletion to have HGF activity, and thus to be able to bind to HGF receptors. That is, the 5 amino acid deletion does not materially effect the properties of the base polypeptide and it is a functional equivalent.

Schwall et al. teach the treatment of various cancers with HGF antagonist antibodies (see claims). In the detailed description at paragraph 23, they teach:

> The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer (small cell and non-small cell), gastrointestinal cancer, liver cancer, kidney cancer, pancreatic cancer, cervical cancer, bladder cancer. hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by increased levels of HGF or overexpression or activation of HGF receptor in the mammal.

Schwall et al. do not teach a method in which a derivative of HGF is used as the antagonist.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a variant of the protein of Date et al. having the 5 amino acid

deletion taught by Nakamura et al. (arriving at a protein having the amino acid sequence of SEQ ID NO: 2), to be used in pharmaceutical compositions as an HGF antagonist, as taught by Date et al. The person of ordinary skill in the art would have been motivated to do so by Nakamura's implicit teachings that the deleted protein was considered to be functionally equivalent to the other form of HGF, and would have expected success for the same reason. Accordingly, the polypeptide of SEQ ID NO: 2 is *prima facie* obvious.

The teachings of Date et al. and Nakamura et al. are summarized above. The combination of these two references renders obvious an HGF antagonist variant or inhibitor protein having the amino acid sequence of SEQ ID NO: 2. In addition to the above teachings, Date teaches in the introduction that HGF is known in the art to be a pleiotrophic growth factor that targets epithelial and endothelial cells, to be involved in branching tubular morphogenesis, tumor invasion, and to stimulate neovascularization in tumors. Date teaches at page 6 that the protein "may have therapeutic potential to prevent invasion and metastasis of various carcinoma cells." Accordingly, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the protein found obvious above over the combination of Date et al. in view of Nakamura et al. to treat cancer or any other medical condition in which neovascularization is a problem, in view of Schwall's teachings, and would have expected success in view of Date's teachings that the protein (without the 5 aa deletion) is an effective HGF antagonist and Nakamura et al., teaching that the 5 amino acid deletion does not affect binding activity, taken with Schwall's teachings of treating a wide variety of cancers with HGF inhibitors. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

Applicant's arguments are not persuasive. One would have been motivated to modify the HGF variant HGF/NK4 polypeptide of Date et al. by making the five amino acid deletion of Nakamura et al. to result in the polypeptide of SEQ ID NO: 2. Given the teachings of Date et al. and Nakamura et al. one of ordinary skill in the art would have expected this polypeptide to be an antagonist with properties similar to HGF/NK4 of Date et al. Nakamura et al. clearly disclose that this five amino acid deletion did not change the HGF properties compared to the untruncated HGF. (See at least Example 4.) Date et al. clearly establish that HGF/NK4 is an antagonist that can inhibit mitogenic, motogenic, and morphogenic properties of HGF. Date et al. clearly suggests that the antagonist could be used to inhibit neovascularization in tumor tissues (see at least page 6). Schwall et al. clearly indicates that HGF inhibitors or antagonists can be used to treat a variety of cancers, including lung cancer, breast cancer (i.e. mammary cancer) and leukemia (i.e. hematopoietic malignancy). Schwall et al. clearly suggests using **any** HGF receptor antagonist that reduces or inhibits the mitogenic or motogenic (migration or scatter) of HGF in the disclosed methods of treatment. (See at least column 5, lines 20-35 of Schwall et al.) The polypeptide of SEQ ID NO: 2 as suggested by the combination of Date et al. and Nakamura et al. would have been expected to have been an antagonist having these properties. As such, it would have been obvious to use the polypeptide of SEQ ID NO: 2 as suggested by the combination of Date et al. and Nakamura et al. in the therapeutic methods of Schwall et al. to treat cancer by inhibition of neovascularization. One would have been motivated to do so with an expectation of success based on the teachings of the prior art.

The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. The skilled artisan would have had reason to try this methodology with the reasonable expectation of success.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/

Primary Examiner, Art Unit 1647

mpa